

Leyman, L., De Raedt, R., Vanderhasselt, M. A., & Baeken, C. (2011). Effects of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex on the attentional processing of emotional information in major depression: A pilot study. *Psychiatry Research*, 185, 102-107.

**Effects of repetitive transcranial magnetic stimulation
of the dorsolateral prefrontal cortex on the attentional processing of emotional
information in major depression: a pilot study.**

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Abstract

Repetitive Transcranial Magnetic Stimulation (rTMS) is as a promising therapeutic tool for major depressive disorder. However, the degree of clinical improvement following rTMS treatment still remains questionable. This pilot study aimed at investigating potential working mechanisms of rTMS by examining the effects on attentional processing towards negative information, a proposed underlying cognitive vulnerability factor for depression. The antidepressant effect of high-frequency (10 Hz) rTMS over the left dorsolateral prefrontal cortex and possible effects on the inhibitory processing of emotional information was assessed in a sample of fourteen depressed patients immediately after the first stimulation session and at the end of a two week treatment period. One session of rTMS caused neither significant self-reported mood changes, nor improvements in inhibitory control towards negative information. After a 10-day treatment period, nine out of our fourteen patients demonstrated significant mood improvements, as indexed by a reduction of more than 50 % on the Hamilton depression rating scale. Responders also demonstrated significant improvements in the inhibitory processing of negative information. This study contributed to the existing evidence of the antidepressant effect of rTMS in the treatment of depression and additionally was able to demonstrate improvements in underlying deficiencies in inhibitory processes towards negative information.

Keywords: major depressive disorder; attention, mood; negative affective priming

1. Introduction

Because of its high prevalence and impact on quality of life, major depressive disorder presents a serious public health concern. Although several therapeutic interventions have proven their effectiveness, some depressed patients (10 up to 20 %) receiving antidepressant medication are partially or totally resistant to treatment (Greenberg et al., 2004). For this group of drug-resistant patients alternative and effective therapeutic options are therefore required. Over the last decade, the application of repetitive Transcranial magnetic stimulation (rTMS) has been proposed as a new promising therapeutic tool for depressive disorder (Rachid and Bertschy, 2006). This non-invasive technique causes disruptions in brain activity by delivering strong magnetic pulses to the cortex that pass through the skull and depolarize the underlying neurons of particular areas in the brain (George et al., 2002).

To date, there has been a flourishing literature on the investigation of possible mood effects of rTMS. Several research groups have provided support for the beneficial antidepressant effect of focal left dorsolateral prefrontal (DLPFC) rTMS in patients with medication-resistant depression. More specifically, improvements in scores on the Hamilton Depression Rating Scale (HAMD: Hamilton, 1960) were demonstrated after two weeks of daily stimulation, which were superior to placebo rTMS treatment (McNamara et al., 2001; Holtzheimer et al., 2002; Kozel and George, 2002; Avery et al., 2006; Bortolomasi et al., 2007). However, despite these promising results, a number of recent studies were unable to replicate the above effects, emphasizing that the degree of clinical improvement still remains questionable (Padberg et al., 1999; Martis et al., 2003; Fabre et al., 2004; Couturier, 2005; Loo and Mitchell, 2005; Schulze-Rauschenbach et al., 2005).

In order to elucidate the above inconsistencies, research should aim at identifying potential underlying mechanisms responsible for the observed mood effects, for instance by investigating accompanying changes in cognitive functioning and information processing.

To date, potential effects of rTMS treatment on cognitive functioning have been primarily evaluated in light of safety concerns (Triggs et al., 1999; Martis et al., 2003). So far, no adverse effect on cognitive performance was found (e.g. Shajahan et al., 2002). Studies measuring cognitions using neuropsychological batteries even indicated significant improvements in response speed, procedural learning, verbal and visuospatial memory and verbal fluency (Padberg et al., 1999; Little et al., 2000; Speer et al., 2001; Martis et al., 2003; Fabre et al., 2004; Hausmann et al., 2004; O'Conner et al., 2005; Schulze-Rauschenbach et al., 2005).

So far, however, no study has specifically focussed on examining the effects of rTMS treatment on specific cognitive dysfunctions in the processing of emotional material. This is puzzling given the clinical and theoretical relevance of the question. Cognitive theories of depression have repeatedly emphasized the role of a biased processing of emotional information in the development and maintenance of depression (Beck et al., 1979; Clark et al., 1999; Beevers, 2005), with recent empirical studies reliably demonstrating a general cognitive inflexibility or inability to inhibit or to disengage from intrusive, irrelevant and negative information, leading to recurrent and remaining patterns of negative thoughts and feelings (Koster et al., 2005; Mogg and Bradley, 2005; Goeleven et al., 2006; Joormann, 2006; Leyman et al., 2007). In line with these findings, recent functional imaging studies have shown disruptions in the prefrontal activation patterns of depressive patients (Mayberg, 1997, 2007; Drevets, 2000; Leppänen, 2006), brain regions found to be important in the implementation of top-down attentional control (MacDonald et al., 2000).

Because focal rTMS can be used to affect neurotransmission and activation patterns within these prefrontal regions (Luborzewski et al., 2007), it may also cause changes in the inhibitory processing of emotional information, which in turn might be an important underlying mechanism causing secondary mood improvement.

Facing this important, but still unanswered research question, the aim of the present pilot study was threefold.

First, this study examined the immediate effects of a single rTMS session over the left dorsolateral prefrontal cortex (DLPFC) on the inhibitory processing of emotional information and mood in treatment-resistant depressive patients during an initial sham-controlled phase. The Negative Affective Priming task (NAP), a well-established experimental paradigm that enables the measurement of the strength of inhibitory processes towards emotional information (Wentura, 1999; Joormann, 2004), was used before and after rTMS. Because recent studies within samples of healthy volunteers have demonstrated that one session of rTMS can induce changes in top-down attentional control (Vanderhasselt et al., 2006a, 2007) and in the inhibition of negative information (Leyman et al., in press), we hypothesized that rTMS would also result in immediate improvements in inhibitory control over negative information in a depressive patient sample. Because improvements in cognitive control in healthy volunteers were not accompanied by acute mood elevations, the latter might be a secondary-order effect only appearing after multiple treatment sessions.

Secondly, the present study also investigated the antidepressive effect of a series of 10 high-frequency (HF) rTMS sessions in a following open trial. Based on previous studies, demonstrating beneficial mood effects after two weeks of rTMS treatment (eg. Avery et al., 2006), in the present study, improvements in depressive symptoms were also expected.

Finally, the third aim of this study was to investigate improvements in the inhibitory processing of emotional information after rTMS treatment. To our knowledge, this study is

the first examining potential changes in the inhibitory control over negative information after two weeks of stimulation, yet, a possible cognitive vulnerability factor underlying depressive onset and recurrence (Linville, 1996; Joormann, 2004; Goeleven et al., 2006).

2. Methods

2.1. Subjects

Fourteen depressed, right-handed patients were selected to participate in this study protocol, which was approved by the local institutional ethics committee of the Academic Hospital (UZ) of the Free University of Brussels and which is in accordance with the latest version of the Declaration of Helsinki.

Prior to inclusion in the study, subjects were carefully screened. All patients met DSM-IV criteria for a current major depressive episode with melancholic features based on the Mini International Neuropsychiatric Interview; a structured clinical interview performed by a trained psychiatrist (MINI) (Pinninti et al., 2003). Six patients reported having a first depressive episode and eight of them had recurrent depressive episodes. Thirteen patients were antidepressant non-responders, ranging in degrees of treatment resistance (TR). Based on the proposed TR staging by Thase and Rush (1997), ten patients could be classified within stage III of TR (i.e. failure of at least two trials of a major class of antidepressants plus failure of an adequate trial of tricyclic antidepressants); three patients were classified into stage V of TR (i.e. failure of a course of bilateral electroconvulsive therapy). For one patient this was the first treatment trial after one year of depression. All included patients underwent a washout of antidepressant medication, monitored by a psychiatrist. At the time of initiation of rTMS treatment, all patients had to be free of anti-depressant pharmacotherapy for at least 2 weeks (minimal 3 weeks for those on Fluoxetine). Only five patients reported the use of anxiolytic agents during treatment (Alprazolam, Flunitrazepam, Clorazepate) and were kept on a steady

dose, whereas nine patients were completely medication free. Importantly, during the rTMS treatment period, all included patients had regular contact with a psychiatrist to evaluate possible deterioration of their mood, but none were receiving additional psychotherapy.

For additional confirmation of diagnosis and assessment of symptom severity prior to rTMS treatment, the 17-item Hamilton depression rating scale was administered (HAMD) (Hamilton, 1960; D'haenen and Verhoeven, 1989), a clinical interview with acceptable validity and reliability reports (Ohara and Rehm, 1983). All participants also completed the Beck Depression Inventory (BDI) (Beck et al., 1961; Bouman et al., 1985), a 21- item, self-report measure of the severity of depressive symptoms, with good reliability and validity reports. Relevant demographic and clinical patient characteristics are summarized in Table 1.

In order to meet safety criteria for HF-rTMS (Wassermann, 1998), patients also underwent a thorough physical and neurological (EEG/MRI) examination. Exclusion criteria were a history of epileptic seizures and neurosurgical interventions, having a pacemaker or other metal or magnetic implants and being pregnant.

Finally, all subjects received a complete description of the procedure of the study and provided written informed consent.

2.2. Study design

Patients underwent 10 sessions of HF-rTMS at the left DLPFC within a period of two weeks (5 days a week). At the beginning of this open treatment trial, each subject also received one placebo (sham) rTMS stimulation session, separated one day from the first active stimulation session. This phase was a randomized crossover, single-blind design allowing examination of short-term, specific rTMS effects in depressive patients.

Potential mood changes were assessed before (T_{pre}), immediately after (T_{post}) and 30 min after (T_{post30}) terminating the first rTMS (real/sham) session, using visual analogue scales.

Antidepressant effects of two weeks of rTMS treatment were investigated using the HAMD and BDI. Inhibitory processing of emotional information was measured before (T_{pre}) and thirty minutes after (T_{post30}) terminating the first rTMS (real/sham) session, and at the end of the rTMS treatment period ($T_{posttreatment}$). Because this study is part of a larger project investigating the influence of rTMS on different neuro-cognitive markers, an additional task was also administered that was not used for the purposes of the present study. This additional measure was a non-emotional task, tapping on different cognitive aspects compared to the task used in the present study (for more information see Vanderhasselt et al., in press). All measures were always presented in the same order for all participants.

2.3. Repetitive Transcranial Magnetic Stimulation (rTMS)

For the application of rTMS we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK) connected to a figure-eight-shaped coil. Before stimulation, the identification of the precise stimulation location of the left DLPFC (Brodmann area 9/46) was determined for each subject using Magnetic Resonance Imaging (MRI) non-stereotactic guidance. More specifically, to obtain individual anatomical information, all subjects underwent a T1-weighted MRI of the brain (3D-TFE, voxel size 1x1x1 mm) using a 1.5T Intera MRI scanner (Philips, Best, The Netherlands). All post processing was done on a viewforum console. Next, the left DLPFC was located visually on the 3D surface rendering of the brain based on the subjects' known gyral morphology, marking the middle part of the median prefrontal gyrus as the centre of the left DLPFC (Brodmann 9/46). The corresponding coil position was marked by determining the perpendicular projection of this point on the scalp. This coil position was held fixed for each rTMS session. Secondly, a stimulation intensity of 110% of the subject's motor threshold of the right abductor pollicis brevis muscle was determined using EMG.

In each high-frequency stimulation session (10 Hz), subjects received forty trains of 3.9 s duration, separated by an intertrain interval of 26.1 s (1560 pulses per session). During sham stimulation, the coil was placed at an angle of 90°, resting on the scalp with only one edge.

During stimulation, all subjects wore earplugs. Before and during stimulation subjects were blindfolded in order to ensure that the altering of the orientation of the coil with respect to the scalp in the placebo condition was effectively blinded.

2.4. Clinical mood assessment

Apart from the assessment of severity of depression symptoms at baseline, the HAMD and BDI were also administered at the end of the rTMS treatment period. In order to evaluate temporary changes in mood, subjects were asked to rate their subjective mood state using five horizontal 100 mm visual analogue scales (VAS) providing measures of sadness, fatigue, tension, anger and vigour (McCormack et al., 1988).

2.5. The Negative Affective Priming Task

Inhibitory processing of emotional information was measured using the Negative Affective Priming (NAP) task (Wentura, 1999; Joormann, 2004). During the administration of the NAP task, subjects were seated at 60 cm viewing distance from an IBM-compatible computer with a 72-Hz, 17-inch colour monitor. The task was programmed using Inquisit software (Millisecond Software, 2001, Version 1.33). At the start of each separate trial, subjects were instructed to look at a fixation cross that was displayed for 1000 ms in the middle of the computer screen. Thereafter, two emotional faces were presented in the upper and the lower half of the screen, one picture surrounded by a grey frame and one by a black frame. At each trial, subjects had to evaluate the valence (positive or negative) of the emotional expression of the target picture in the grey or black frame (randomized across

subjects) by pressing one of two corresponding keys and had to ignore the distractor picture. In this multi-stimulus task, a complete NAP sequence includes two separate trials: a prime and a probe trial, both trials being separated by an intertrial interval of 1000 ms (+ 1000 ms fixation cross). Importantly, participants were not aware of this difference between prime and probe trial. However, within experimental conditions, distractors in the prime trial correspond with the emotional valence of targets in the probe trial. Due to this manipulation, the negative affective priming effect can be measured, involving a slowdown in responding to an item that has previously been inhibited, a valid index of inhibitory functioning toward affective material. This delay in responding is not expected within control conditions, in which there is no similarity between prime and probe. Table 2 provides an overview of the different conditions used in the NAP task.

Subjects first completed 32 practice trials, followed by a sequence of 256 test trials, divided into 8 blocks of 16 prime and probe trials. The sequence of trials within the blocks was randomized, as was the spatial position of the target and distractor. The entire task lasted approximately 20 minutes. The 88 coloured pictorial stimuli used in this paradigm were carefully selected on valence and arousal ratings based on a prior validation study of the Karolinska Directed Emotional Faces database (Goeleven et al., 2008). In the present task, 33 happy, 33 sad and 22 neutral faces were presented in random order. The neutral faces were used as distractors in the probe trials. Facial expressions were 5 cm wide by 5.5 cm high and were surrounded by a 3 mm coloured frame. Responses to prime and probe trials were recorded, but only responses to the probe trials were analyzed.

3. Results

For all analyses the significance level was set at an alpha level of 0.05. Analyses were conducted with SPSS 12.0.

3.1. Short-term effects of rTMS on mood and attention

Mean mood ratings reported before (T_{pre}), immediately (T_{post}) and 30 min after (T_{post30}) terminating the first rTMS session (stimulation: active or sham) are summarized for each VAS in Table 3. Due to missing values on the VAS reports, two subjects were removed from analysis. Separate analysis of variance (ANOVA), with repeated measures (multivariate approach) for each VAS scale showed no main effects for stimulation on reports of anger ($F < 2$) or for the other mood scales (all F s < 1). No significant overall effects of time were found on reports of fatigue ($F(1,11) = 2.95$, $P = 0.1$), anger ($F(1,11) = 2.40$, $P = 0.14$), depression ($F(1,11) = 2.02$, $P = 0.18$), vigour and tension (F s < 1). Finally, also the crucial interaction effects between stimulation and time did not reach significance (all F s < 1.5). These results indicate that one single session of rTMS had no effect on mood.

An ANOVA with valence (negative vs. positive), stimulation (sham vs. rTMS) and time (T_{pre} vs. T_{post30}) as within-subject factors was performed on the NAP scores (individual mean reaction times in the experimental condition minus individual mean reaction times in the control condition) to examine immediate effects on the attentional processing of emotional information. A positive NAP score indicates effective inhibition of emotional information, whereas the smaller this score, the more inhibitory control becomes impaired. Contrary to our expectations, the three-way interaction effect between valence, stimulation and time was not significant ($F < 1$). We also could not demonstrate a significant main effect of stimulation or time (F s < 1), nor did we find any significant two-way interaction (all F s < 1.5). However, a near significant main effect of valence was found, $F(1,13) = 3.80$, $P = 0.07$, revealing a more effective inhibitory control for positive facial expressions (Mean = 36 ms) compared to the negative faces (Mean = - 0.45 ms). To conclude, these results indicate that one single session of rTMS also had no immediate effect on the attentional processing of emotional information.

However, we could demonstrate that depressed patients showed overall lower inhibition for negative as compared to positive faces.

3.2. Treatment response

After two weeks of rTMS treatment the whole patient group showed an overall reduction of 43.8 % of their scores on the HAMD and a reduction of 21.7 % on the BDI. Nine out of fourteen patients (64.3%) showed a reduction of more than 50 % of their scores on the HAMD. This way, patients were divided into two groups: responders and non-responders. Individual ratings on the HAMD and BDI for responders and non-responders, group means before and after rTMS treatment and the mean change percentage on the HAMD and BDI for each group are presented in Table 4.

Examination of changes in BDI scores using a 2 X 2 ANOVA with time (T_{pre} vs. $T_{posttreatment}$) as within-subject variable and treatment response (responders vs. non-responders) as between-group factor revealed a main effect of time ($F(1,12) = 10.00, P < 0.01$) which was indicative of a significant decrease in depressive symptoms after two weeks of rTMS treatment across patients. Moreover, we also established a significant main effect of treatment response ($F(1,12) = 9.09, P = 0.01$) as well as a two-way interaction effect between treatment response and time ($F(1,12) = 8.89, P = 0.01$). Non-parametric tests were used (due to the small sample sizes) to further investigate this effect within groups of responders and non-responders (Wilcoxon Signed-Rank test). Within the group of responders, significant lower BDI scores were reported after treatment compared to baseline ($z = 2.67, P < 0.01$), whereas this was not the case for non-responders ($z = 0.13, P = 0.89$).

3.3. Effects of rTMS treatment on attention

To examine the effects of rTMS treatment on measures of inhibitory processing of emotional information, an ANOVA with valence (negative vs. positive) and time (T_{pre} vs. $T_{posttreatment}$) as within-subject factors and treatment response (responders vs. non-responders) as between-subject factor was performed on the NAP scores. Pre-measures of inhibitory control were for each subject based on their first administration of the NAP task (which was either before active or sham stimulation). Analyses revealed a near significant three-way interaction effect ($F(1,12) = 3.58, P = 0.08$). No other main effects or interactions were significant (all $Fs < 1.6$).

In order to further explore the established three-way interaction, changes in attentional processing were investigated within groups of responders and non-responders, using non-parametric tests (Wilcoxon Signed-Rank test). Within the group of responders, mean NAP scores for negative information increased significantly after HF-rTMS treatment (Mean $T_{pre} = -87.77$ ms vs. Mean $T_{posttreatment} = 5.92$ ms) ($z = 1.60, P = 0.05$ – one tailed). Contrary, no significant changes in inhibitory control for negative information were found in the non-responders (Mean $T_{pre} = -1.09$ ms vs. Mean $T_{posttreatment} = -76.18$ ms) ($z = 1.21, P = 0.11$ – one tailed). In both groups, no significant changes in inhibitory control for positive information were found ($z < 1$).

3.4. Correlation of clinical mood changes and changes in attentional processing

In order to investigate whether improvements in depressive symptoms after HF- rTMS treatment were associated with changes in the inhibition of emotional information (i.e. posttreatment-measures minus pretreatment-measures of the inhibition scores for sad and happy facial expressions), Pearson correlation coefficients were calculated over the whole group.

A significant positive correlation was found between changes in BDI scores and changes in inhibition scores for sad faces ($r = 0.64$, $P < 0.05$), indicating that improvements in mood after treatment were associated with improvements in the inhibition of negative information. However, examining correlations between changes in BDI scores and changes in inhibition scores for positive faces, no significant results were found ($r = 0.04$, $P = 0.88$).

4. Discussion

The present pilot study aimed at offering a first glance at the potential effects of left dorsolateral prefrontal HF-rTMS on the attentional processing of emotional information in a sample of depressive patients both immediately after cessation of stimulation and at the end of a two week treatment period. Two important findings were established. A single session of HF-rTMS did not result into improved inhibitory processing of negative information nor into significant mood improvements. However, at the end of a treatment period of two weeks, in most of the patients, a decrease in depressive symptoms was found to be associated with improved inhibitory control for negative information. These results will be discussed in more detail below.

In line with several previous reports (Avery et al., 2006; Rachid and Bertschy, 2006; Bortolomasi et al., 2007; Herwig et al., 2007; O'Reardon, 2007) this study was able to demonstrate a mean reduction in scores on the HAMD scale of 43.8 % after two weeks of rTMS treatment. For more than half of our depressive patient sample (64 %) this implicated a reduction of more than 50 % of their scores, with beneficial effects of rTMS treatment also reported on self-report measures of depressive symptoms (i.e. a mean change of 21.7 % on the BDI). The high percentage of mood improvement in this depressive patient sample - compared to previous studies investigating mood effects after rTMS treatment (e.g. Couturier, 2005) - can possibly be attributed to some methodological advantages of the present study.

First, a more intensive treatment protocol was used compared to prior studies (e.g. Koerselman et al., 2004), with high stimulus frequencies (10 HZ), high stimulus intensities (motor threshold above 110 %) and more and frequent pulses (1560 pulses per session), probably having greater antidepressant potency. Secondly, apart from the potential dose-response effect, the higher response rate in the present study may also be attributed to the use of the MRI guided identification procedure of the left DLPFC. This method allowed taking variability in head size and shape into account in order to prevent missing the precise stimulation location of the left DLPFC.

Although clear antidepressant effects were established after two weeks of rTMS treatment, the present study was unable to demonstrate similar positive mood changes immediately after one single session of rTMS. The present results are in contrast with previous findings of acute mood elevations after a single rTMS session in subjects experiencing major depression (Szuba et al., 2001), yet, these results have not been replicated to date. Conversely and in line with the present findings are results from recent studies examining immediate mood effects of rTMS in healthy volunteers. These studies also failed to demonstrate significant mood changes immediately after cessation of stimulation (Mosimann et al., 2000; Baeken et al., 2006), stating that one stimulation session may be too short to induce changes in the neurotransmission related to antidepressant response.

Apart from the investigation of possible antidepressant mood effects of rTMS treatment, this pilot study was the first to additionally evaluate the impact of HF-rTMS over the left DLPFC on the attentional processing of emotional material. In line with previous cross-sectional research of inhibitory functioning in depressive patient samples (Linville, 1996; Joormann, 2004; Goeleven et al., 2006), this study was able to demonstrate a pattern of results indicative of an impaired inhibitory control for sad facial expressions before HF- rTMS treatment as compared to positive information. This disturbance in the attentional processing

of negative information in depressive patients is not a unique finding and has already been reported within a number of recent studies reliably demonstrating maintained attention towards depression-related information and difficulties in disengaging attention away from emotional information with a negative content (e.g. Koster et al., 2005; Leyman et al., 2007). However, when evaluating the immediate effects of one single session of rTMS on this dysfunctional attentional processing, no instant improvements in inhibitory control were found, contrary to our expectations based on recent reports of enhanced top down attentional control (Vanderhasselt et al., 2006a, 2006b, 2007) and immediate changes in the inhibitory processing of negative information after prefrontal HF- rTMS in healthy volunteers (Leyman et al., in press). Yet, based on theoretical assumptions made by cognitive theories of depression (e.g. Beck et al., 1979), a possible explanation for these null results can be proposed. According to Beck (2008), impairments in attentional functioning and inability to filter out negative information are not just simple state markers of depression, but may remain present beyond episodes of depression as also reported in recent research (e.g. Joormann and Gotlib, 2007). This continuous cognitive inflexibility is likely to be associated to functionally related brain structures such as the DLPFC that may not be susceptible to immediate modifications but nonetheless can be targeted by means of repeated transcranial stimulation (e.g. Luborzewski et al., 2007). Contrary, inducing changes in blood flow and regional metabolism within prefrontal brain regions in groups of healthy subjects might lead to immediate, yet transitory changes in cognitive functioning. Based on this reasoning, future research should aim at continuously monitoring inhibitory processing and accompanying changes in brain activation patterns (eg. using fMRI) during the entire course of rTMS treatment in order to shed light on possible causal effects.

Finally and perhaps the most important finding of the present study was that, within the group of participants who reported significant mood improvements after two weeks of HF-

rTMS treatment, their disturbed inhibition of negative information also improved significantly. These improvements were not established within our group of non-responders, nor were they found for positive information processing. Moreover, positive changes in inhibition scores for sad faces were significantly correlated with decreases in scores on the BDI. The present results are consistent with previous findings of improvements in general cognitive performance after rTMS treatment in depressive patient samples (Fabre et al, 2004; Hausmann et al., 2004; O'Conner et al., 2005; Schulze-Rauschenbach et al., 2005) and extend these positive effects to the processing of emotional material. Importantly, because improved inhibitory processing of negative information was only established in those patients who showed a significant antidepressant effect after treatment, our results are also indicative of the possibility that rTMS-induced mood improvement may to some extent be related to improvements in cognitive functioning.

Although the above findings are promising, some important limitations of the present pilot study need to be addressed.

First, this study used an open trial of depressed patients. Therefore, because of the absence of a control group within the multi-session part of the design, possible placebo responses or practice effects on task performance cannot be excluded. Moreover, due to the absence of a control group, the established mood improvements after two weeks of rTMS treatment in nine of our depressed participants could have been a simple reflection of normal mood improvements over time. This may cause a need for appropriate caution in interpreting the present findings. However, because our study sample almost completely consisted of medication-resistant depressive patients who were already confronted with multiple failures of antidepressant treatment trials in the past and reported long periods of depression, spontaneous responses would be unexpected. Furthermore, administering placebo rTMS during a period of two weeks in a comparable sample of treatment-resistant depressive

patients, who consequently also have to undergo a washout of antidepressant medication, was not feasible from an ethical point of view.

A second important limitation was the small sample size involved in the present study. Due to this limitation we were unable to check, using regression analysis, whether changes in mood after rTMS treatment remained when controlling for changes in inhibitory processing of emotional information. In other words, this pilot study was unable to provide evidence of specific responder characteristics, related to the attentional processing of emotional information that might be predictive of future treatment response. Therefore, in order to elucidate this question, future research should aim at replicating this study using larger sample sizes. Former research has already been conducted in determining whether specific biographical, clinical or psychopathological parameters are associated with the antidepressant response to rTMS (Brakemeier et al., 2007), however, not specifically focussing on this important cognitive vulnerability marker.

In conclusion, although the data presented in this study are preliminary and await future replication, due to the small sample size and absence of a placebo control condition, this pilot study was the first exploring possible effects of rTMS treatment on the dysfunctional inhibitory processing of negative information, a frequently reported cognitive bias underlying the onset and recurrence of major depressive disorder. Future research involving larger numbers of patients and including a sham-controlled condition is needed to further investigate possible primary and second-order effects of rTMS treatment in depression.

Acknowledgements

This research was supported by a grant from the Scientific Fund W. Gepts AZ-VUB.

The authors wish to thank Professor Hugo D'haenen for his assistance with the study design and recruitment of the depressive patient sample and regret his sudden decease.

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Table 1. *Demographic and clinical patient characteristics at baseline.*

Variable (N = 14)	
Age	44.3 (7.55)
Gender ratio (M/F)	4/10
Hamilton Depression Score (HAMD)	23.5 (4.31)
Beck Depression Inventory (BDI-I)	31.71 (7.92)
Age at onset (years)	34.07 (11.36)
Duration of current depressive episode (years)	4.5 (4.91)
% Hospitalisation	64%
% High suicide risk*	43%

Note. Standard deviations are shown in parentheses. * Based on criteria from the Mini International Neuropsychiatric Interview (A high suicide risk comprises of ‘*making plans to commit suicide*’ or ‘*tried to commit suicide*’ or a combination of ‘*thoughts of suicide*’ and ‘*past suicidal attempts*’).

Table 2. *Control and experimental conditions for negative and positive trials in the NAP task*

	Negative trials		Positive trials	
	Control	Experimental	Control	Experimental
Prime Trial				
Distractor	+	-	-	+
Target	+	+	-	-
Probe Trial				
Distractor	N	N	N	N
Target	-	-	+	+

+ happy facial expression, - sad facial expression, N neutral facial expression.

Table 3. *Mean ratings and standard deviations for the VAS measures before (T_{pre}), immediately (T_{post}) and 30 min after (T_{post30}) rTMS (active or sham stimulation).*

	Active (N = 12)			Sham (N = 12)		
	T_{pre}	T_{post}	T_{post30}	T_{pre}	T_{post}	T_{post30}
VAS						
Depression	5.89 (3.17)	5.46 (3.61)	5.92 (3.52)	6.19 (3.17)	5.08 (3.30)	5.21 (3.40)
Anger	1.66 (2.04)	0.87 (1.19)	0.85 (0.91)	1.20 (1.46)	0.53 (0.58)	0.54 (0.58)
Tension	5.03 (2.98)	4.21 (3.71)	4.36 (3.60)	4.38 (2.88)	4.30 (3.24)	4.51 (3.16)
Fatigue	6.33 (3.40)	6.91 (3.06)	7.77 (2.78)	7.19 (1.88)	6.98 (1.13)	7.41 (2.48)
Vigor	1.82 (1.91)	1.79 (1.75)	1.53 (1.37)	1.59 (1.05)	1.56 (0.85)	1.50 (1.22)

Table 4. *Individual scores and group means on the Hamilton Depression rating scale (HAMD) and Beck Depression Inventory (BDI-I) before and after rTMS treatment for responders and non-responders.*

	HAMD		BDI-I	
	Pre – rTMS	Post – rTMS	Pre – rTMS	Post – rTMS
<i>Responders (n = 9)</i>				
1	21.0	6.0	23.0	17.0
2	26.0	9.0	38.0	23.0
3	27.0	6.0	17.0	6.0
4	27.0	10.0	26.0	21.0
5	25.0	8.0	33.0	10.0
6	27.0	12.0	41.0	16.0
7	20.0	4.0	31.0	13.0
8	12.0	3.0	33.0	26.0
9	23.0	9.0	32.0	19.0
Mean (SD)	23.1 (4.9)	7.4 (2.9)	30.4 (7.4)	16.8 (6.4)
Mean Change Percentage (%)		67.96		44.74
<i>Non-responders (n = 5)</i>				
10	29.0	34.0	49.0	40.0
11	23.0	17.0	32.0	36.0
12	20.0	11.0	24.0	36.0
13	25.0	16.0	33.0	23.0
14	24.0	18.0	32.0	33.0
Mean (SD)	24.2 (3.3)	19.2 (8.7)	34.0 (9.1)	33.6 (6.4)
Mean Change Percentage (%)		20.66		1.18

Note. Standard Deviations are shown in parentheses.

